REMARKS

Applicants wish to thank the Examiner for withdrawing the written description rejection against claims 58 – 60. Please reconsider the present application in view of the above amendments and the following remarks.

Disposition of the claims

Claims 1 – 8, 11, 19, and 58 – 60 are currently pending. Claims 1, 7 and 8 are independent. Claims 2 – 6, 11, 19 and 58 depend, directly or indirectly, from claim 1. Claim 59 depends from claim 7. Claim 60 depends from claim 8. Claim 1 has been amended in this Reply.

Amendment to the claims

Claims 1, 2, 4-8 and 58-60 are amended. Claims 1, 7 and 8 have been amended to clarify that the isolated RNA comprises an artificial intron that comprises a gene silencing effector that, when released in a cell silences the function of a target gene. Support for this amendment can be found, for example, in Figure 1 of the specification and the associated text. Applicants note that no new matter has been introduced by the foregoing amendments.

Rejections under 35 U.S.C. §102

Claims 1, 2, 3, 7 and 11 stand rejected as being anticipated by Cheo et al. (US 7,393,632). Independent claims 1 and 7 have been amended in this Reply. To the extent that this rejection may still apply, Applicants respectfully traverse this rejection.

With respect to independent Claim 1, the claim has been amended to recite:

> An isolated RNA comprising:
> an **artificial intron comprising a gene silencing effector,**
> wherein when the **artificial intron is released in a cell**, the function of a target gene is silenced.

Applicant respectfully submits that present claim 1 patentably distinguishes over the cited art. It is one unexpected discovery of the present invention that introns may be used as a delivery vehicle for delivering a gene silencing effector sequence such as a hairpin gene-silencing sequence. Similar to the use of plasmids as a vector for carrying genes, one embodiment of the present invention inserts a **gene silencing effector** into an intron to form **an artificial intron**. The artificial intron, when released into a cell, will be processed by the intron processing mechanism of the cell, during which the gene-silencing effector insert is activated to silence a target gene.

The Office alleges that Cheo discloses a method for inducing RNA splicing/processing-associated gene silencing effects in cultured eukaryotic cells which meets each and every element of Claim 1. In particular, the Office cites Examples 13, 14, and Figure 20D of Cheo as specifically teaching gene-silencing artificial RNA that can be removed using intron/exon splicing sequences. Applicants respectfully disagrees.

First, Cheo does not teach or suggest any **artificial intron comprising a gene silencing effector**. Cheo is primarily concerned with a method of recombinational cloning and its various applications. While Cheo discusses the production of gene-silencing molecules, it is limited to the use of its recombinational cloning method for constructing vectors that will directly express the gene silencing effectors (such as RNAi, antisense RNA, etc). Where Cheo discusses the use of

intron/exon splicing sites, it is for the purpose of removing unwanted nucleic acid segments intervening two desired segments, not to form artificial introns carrying gene silencing effectors.

For example, in Example 13, Cheo prefaces its discussion by stating that

> "As explained below, in one aspect, the invention provides methods for removing nucleotide sequences encoded by recombination sites from RNA molecules. One example of such a method employs the use of intron/exon splice sites to remove RNA encoded by recombination sites from RNA transcripts." (col. 133, ll. 5 – 9).

Thus, when read in context, Cheo Example 13 is directed to the use of intron/exon splice sites as a tool to excise unwanted fragments introduced into the RNA transcript because of the recombination sites. In this case, the portion flanked by the exon/intron splicing sites is to be discarded as junk, NOT as a purposely designed artificial intron, much less one that contains a gene silencing effector.

It is noted that Example 13, in the paragraph between lines 18 – 28 (col 134), mentions "antisense RNA". However, this section teaches that one may produce an "antisense-ribozyme" construct using its recombinational cloning method to achieve gene silencing effect (col. 112, ll. 46 – 58). However, the recombinational cloning method will not directly result in the desired construct, but a construct with a recombination attachment site in between the two desired parts of the transcript. Cheo proposes using exon/intron splicing sites to excise this unwanted intervening sequence to arrive at the desired "antisense-ribozyme" construct. In this case, the gene-silencing effector is still encoded outside of the artificial intron (the junk region flanked by the intron/exon splicing sites). When read as a whole, one of ordinary skill in the art would understand that Example 13 of Cheo does not teach or suggest any **artificial intron comprising a gene-silencing effector**.

Similarly, Example 14 also teaches using intron/exon splice sites as a tool to remove unwanted att sites from RNA transcripts. Cheo states in Example 14 that

> "The above describes some applications of RNA splicing with the GATEWAY™ system, which is to remove attB1 between ORF and N-terminal sequences and to remove attB2 sequences between ORF sequences and C-terminal sequences of protein fusions....Further, one such application is the use of the RNA splicing process to remove att sequences interposed (as a result of performing a GATEWAY™ recombination-based subcloning reaction) between sequences encoding multiple protein domains in a eukaryotic expression vector, where the ORFs encoding the various domains are separated by an att site sequence." (col. 137, ll. 9 – 20).

From the above, it is clear that Cheo's use of intron/exon splicing is only for removing unwanted segments interposed between desired domains as a result of recombination cloning. There is no teaching or suggestion of any **artificial intron comprising a gene-silencing effector**.

As for Figure 20D, that figure shows a schematic representation of a vector containing two DNA inserts having the same nucleic acid sequence in opposite orientations. Using a T7 promoter, the two oppositely oriented sequences are transcribed as a single RNA transcript. The resulting RNA transcript will then undergo intramolecular hybridization to form a hairpin loop (col. 46, ll. 23 – 33). Figure 20D cannot anticipate claim 1 because it does not contain any artificial intron. Moreover, the T7 promoter is a bacterial promoter. It is well-known in the art that bacteria are prokaryotic cells and do not have intron/exon splicing capability. Therefore, one of ordinary skill in the art would understand that Figure 20D does not teach or suggest any artificial intron encoding a hairpin gene-silencing RNA because the T7 promoter will not work in a eukaryotic system, which is required for intron/exon splicing.

In view of the above, Applicants submit that independent claim 1 is patentable over Cheo for at least the reason that Cheo fails to teach or suggest any **artificial intron comprising a gene-silencing effector**. Claims 2, 3, and 11 depend from claim 1 and are patentable for at least the same reasons as claim 1. Withdrawal of the rejection and allowance of claims 1-3 and 11 is respectfully requested.

Independent claim 7 also recites the same **artificial intron comprising a gene-silencing effector** limitation. Therefore, for at least the same reasons set forth above, claim 7 is also patentable over Cheo. Withdrawal of the rejection and allowance of claim 7 is respectfully requested.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. §103

Claims 1 – 8, 11, and 19 stand rejected under 35 U.S.C. §103 as being unpatentable over Cheo et al in view of Mitchell et al. (US 6,013,487), Krawczak et al. (Hum Genet 1992, Vol. 90: 41-54), Zhuang et al. (PNAS Vol. 86: 2752-2756) Coolidge et al. (Nucleic Acid Res., 1997, Vol. 25, No. 4:888-896) and Bennett et al. (US 6,710,174). Applicants respectfully traverse this rejection.

The Examiner alleged that Applicants previous arguments merely attacked the cited references individually and do not consider them as a combination. Applicants respectfully disagree. As explained above, the primary reference Cheo fails to teach or suggest at least the limitation that the isolated RNA of the present invention has **an artificial intron comprising a gene-silencing effector**. In Applicants' previous Reply, Applicants reviewed the teachings of each cited references in combination with Cheo to illustrate that none of them can cure the defect of Cheo. That reply is incorporated herein by reference. Insofar as none of the cited references teaches or suggests that a gene-silencing effector can be

encoded within an artificial intron to effect gene-silencing, their combined teachings still cannot yield this insight. Nor has the Office made any other showing, based on references or the knowledge of those of ordinary skill, that would indicate the invention would have been obvious to a person of ordinary skill.

In view of above, Applicants submit that the combination of Cheo, Mitchell, Krawczak, Zhuang, Coolidge, and Bennett fails to render independent claims 1, 7 and 8 *prima facie* obvious for at least the reasons set forth above. Therefore, claims 1, 7, 8, and their dependent claims 2 – 6, 11 and 19 are all patentable over the combination of Cheo, Mitchell, Krawczak, Zhuang, Coolidge, and Bennett.

Accordingly, withdrawal of this rejection is respectfully requested.

Claims 58 – 60 stand rejected under 35 USC §103 as being unpatentable over Cheo et al in view of Mitchell et al. (US 6,013,487), Krawczak et al. (Hum Genet 1992, Vol. 90: 41-54), Zhuang et al. (PNAS Vol. 86: 2752-2756) Coolidge et al. (Nucleic Acid Res., 1997, Vol. 25, No. 4:888-896) and Bennett et al. (US 6,710,174). Applicants note that claims 58 – 50 are dependent claims 1, 7 and 8, respectively. For at least the same reasons that the combination of Cheo, Mitchell, Krawczak, Zhuang, Coolidge, and Bennett cannot render the independent claims obvious, claim 58 – 60 are also patentable over these references.

Accordingly, withdrawal of this rejection is also respectfully requested.

CONCLUSION

Applicant believes the foregoing amendments comply with requirements of form and thus may be admitted under 37 C.F.R. § 1.116(b). Alternatively, if these amendments are deemed to touch the merits, admission is requested under 37 C.F.R. § 1.116(c). In this connection, these amendments were not earlier

presented because they are in response to the matters pointed out for the first time in the Final Office Action.

Lastly, admission is requested under 37 C.F.R. § 1.116(b) as presenting rejected claims in better form for consideration on appeal.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (310) 595-3000 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 07-1896.

Respectfully submitted,
DLA PIPER LLP (US).

Date: November 12, 2010

By: /mcl/
Matthew C. Lee, Ph.D.
Registration No. 58,189
Patent Agent for Applicant(s)

1999 Avenue of the Stars, Suite 400
Los Angeles, California 90067
Telephone: 310-595-3000
Facsimile: 310-595-3300